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The effect of lidocaine on TRPM 2,6,7 and 8 channels in liver ischemia / reperfusion model in rats

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Abstract
Aim: The transient receptor potential melastatin (TRPM) channel is subfamilies of the transient receptor potential (TRP) channels, cation permeable channels. Ischemia and reperfusion (I / R) injury is a phenomenon highlighting cellular damage of the liver caused by oxygen. Lidocaine is a local anesthetic that blocks sodium channels and suppresses mitochondrial functions of neutrophils. In this study, we purpose to investigate the effects of TRPM2/8 and TRPM6/7 expressions after lidocaine treatment in liver ischemia/reperfusion rat model.
Materials and Methods: The study was carried out on 32 male Wistar rats. The animals were randomly divided into 4 groups including sham, lidocaine, I/R group and I/R- lidocaine group. The portal vein and the hepatic artery branches were clamped for 60 minutes for complete ischemia. TRPM2/8 and TRPM6/7 gene expression levels were assessed by RT-qPCR.
Results: The expression levels of TRPM2 were significantly higher in liver-I/R group compared to sham and lidocaine groups ($p<0.05$, $p<0.000$, respectively), TRPM8 genes were significantly higher in liver-I/R group compared to sham and lidocaine groups ($p<0.05$, $p<0.05$, respectively). However, the expression levels of TRPM6 gene was significantly higher in liver-I/R group compared to sham, lidocaine, and I/R-lidocaine groups ($p<0.05$, $p<0.01$, $p<0.05$, respectively), TRPM7 genes was significantly higher in liver-I/R group compared to sham, lidocaine and I/R-lidocaine groups ($p<0.05$, $p<0.000$, $p<0.05$, respectively).
Discussion: In conclusion, we firstly showed that an association between the expression level of TRPM2/8, TRPM6/7, and hepatic I/R, I/R-lidocaine groups as well as TRPM2/8 and TRPM6/7 gene expressions are affected by lidocaine in the liver-I/R in a rat model.

Keywords
Sodium channel; Ischemia; Reperfusion; TRPM; Lidocaine

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Introduction

The transient receptor potential (TRP) channels are a form of calcium channels and they transport magnesium, calcium, trace metal ions and modulate the driving force for ion entry [1, 2]. TRPs are present in all cellular membranes, with the exception of the nuclear envelope and mitochondria [3]. TRPs are localized in the plasma membrane and almost every cell type expresses them [2]. TRPs multigene superfamily encodes integral membrane proteins and is divided into seven subfamilies: TRPC (canonical), TRPM (melastatin), TRPV (vanilloid), TRPA (ankyrin transmembrane protein), TRPML (mucolipin), TRPN (nom PC-like) and TRPP (polycystin), [4]. The members of the TRPM family (Melastatin) were divided into 4 groups according to the sequence similarity (TRPM1 / 3, TRPM2 / 8, TRPM4 / 5 and TRPM6 / 7) [4]. TRPM2 is most commonly expressed in the brain but is found in various peripheral cell types. TRPM2 is also suggested to play a role in oxidative stress / reactive oxygen species, TNF-α mediated Ca2+ influx and cell death [5]. TRPM6 and 7 show high permeability to Ca2+ and magnesium. In accordance with the role of TRPM6 in Mg+2 homeostasis, the decrease in intracellular Mg+2 concentrations activate the channel [6]. TRPM7 also plays a role in the regulation of neuronal cell death and cell cycle [7]. TRPM8 is activated by cooling (<26˚C) and by menthol. TRPM8 was originally cloned from human prostate but is also expressed in many types of tumor tissues, such as breast, colon, lung, and skin [8].

Intracellular calcium has been described as an important secondary messenger ion, and high calcium concentration leads to compressive compensatory vasodilatation after a vasoconstriction period [9]. All of these causes, including lack of oxygen and nutrients, initiate apoptosis and necrosis [10]. Ischemia and hypoxia cause failed permeability of cell membranes leading to a high level of free intracellular calcium which causes ischemic liver tissue injury. Liver ischemia-reperfusion (I/R) remains a major problem after partial hepatectomy and transplantation [11, 12].

Lidocaine is a local anesthetic that blocks sodium channels, shows anti-inflammatory effects due to its ability to inhibit superoxide formation and leukocyte metabolic activity [13]. Thus, lidocaine is effective for flap recovery after reperfusion injury [14]. The voltage-clamped studies showed that increasing the calcium in the external medium affects sodium and potassium conductance versus voltage curves. Moreover, treatment with a high calcium leads to an increase in the time to peak of the sodium level [15]. Thus, our hypothesis is that the sodium channel blocker (lidocaine) affects calcium level or calcium channels or vice versa.

There is a limited study on the use of sodium channel blockers to prevent ischemia- reperfusion liver injury. However, there are few studies on the relationship between sodium channel blocker administration and TRPM channels [9]. To understand the roles of TRPM calcium channels in liver tissue is important to explain the pathogenesis of ischemia- reperfusion and membrane depolarization. Thus, we purpose to investigate the effects of TRPM2/8 and TRPM6/7 expressions after treatment of sodium channel blocker (lidocaine) in a rat model with hepatic ischemia-reperfusion.

Material and Methods

Experimental Design

The study was carried out on 32 male Wistar rats (average weight 225±25) housed in an environmentally controlled room (240C to 260C temperature) with a 12:12 hour light: dark cycle, and kept on commercial rat chow and tap water ad libitum. The Committee on the Ethics of Animal Experiments of the Mustafa Kemal University has approved the study protocol.

The animals were randomly divided into 4 groups including sham, lidocaine, I/R group and I/R- lidocaine (sodium channel blocker) group.

Sham Group: Rats were pretreated with saline solution and surgical procedures, except for induction of liver ischemia, but including liver resection (n=8).

Sodium channel blocker (Lidocaine) group: The rats were treated with lidocaine as pretreatment (5 mg/kg) [16] and none of the rats was applied ischemia-reperfusion (n=8).

Ischemia-reperfusion group (I/R): Rats were not treated by any substance. For Ischemia atraumatic vascular vein and right hepatic artery were clamping for 60 minutes after the laparotomy. After reperfusion, all group members underwent relaparotomy and the livers were isolated (n=8).

Ischemia-reperfusion/sodium channel blocker (I/R-lidocaine) group: Lidocaine (5 mg/kg) was given orally to the rats 30 minutes before anesthesia as pretreatment. Xylazine/ ketamine (12/80mg/kg) was administered as anesthetic protocol. Ischemia was performed with a clamp on the portal vein and left lateral branches of the hepatic artery for 60 minutes after laparotomy. Relaparotomy was performed in all group members and livers were isolated for 60 minutes after reperfusion (n=8) [6].

Surgical Procedures

The rats were anesthetized by using xylazine/ ketamine (12/80mg/kg) combination and placed in a supine position on a temperature-controlled heating table, maintaining the body temperature in the range of 36.5-37.50C. The rats were allowed breathing spontaneously during surgery. For the preparation of the liver, abdominal skin was sterilized with ethyl alcohol (70 %) and shaved. Then, using subcostal incisions and midline laparotomy, the liver was carefully mobilized from all ligamentous attachments. The left lateral branches and portal of the hepatic artery were clamped for 60 minutes in an atraumatic vascular clamp. The abdominal incision lines were closed to the margin and wetted with isotonic saline to accompany those who had removed excess body fluids. The median and left hepatic lobes were taken and then the abdomen was favorably watered with isotonic saline after extraction of the clamp. During I/R periods, the abdomen was covered with a plastic wrap to minimize fluid loss via evaporation. At the end of the first hour of reperfusion, the abdomen was closed by continuous stitches using Vicryl (Ethicon Endo-Surgery, Inc. USA) 4/0 sutures and the animals were returned to their cages. After 60 minutes of reperfusion, animals were anesthetized with an intraperitoneal injection of xylazine/ ketamine (12/80mg/kg) and were sacrificed, then histological samples were taken for RT-PCR and histopathological examination [6, 9].

Gene expression analysis (qRT-PCR)

Total RNA was isolated by using kits (RNAeasy Kit, Qiagen, Germany). cDNA was procured using the reverse transcription

assay kit (cDNA RT. Kit, USA). Shortly, 10X RT random primers (2 µl), 10X buffer reverse transcriptase (2 µl), dNTP mix (0,8 µl) (Table 1), AMV RT. (1 µl), RNase and mRNA free water (4,2 µl) were mixed to procure cDNA. The reaction admixture was incubated at 250C for 10 minutes and 370C for 120 minutes for reverse transcription and heated at 850C for 5 minutes to inactivate AMV reverse transcriptase. cDNA procured was stored at -200C until tested. Then, cDNA was denatured at 950C for 10 minutes, at 950C for 15 seconds annealed at 600C for 1 minute (TRPM2/8, TRPM6/7), and extended at 950C for 3 minutes and at 720C for 30 seconds. The reaction admixture was exposed to 40 cycles of PCR after an initial 15 seconds denaturation step at 950C. Expressions of TRPM and p-actin mRNA as the cleaning gene were analyzed by quantitative reverse transcriptase PCR in Rotor-Gene Q (QIAGEN Rotor-Gene Q, Germany). Primary sequence information of the gene regions used in the study is given in Table 1.

Table 1. Primary sequence information of the gene regions.

Gene		Primary Sequences Used	Tm	Length (bp)
TRPM2	Left	5'-AAT TTG CTC ATC GCC ATG TT-3'	53.2	20
TRPM2	Right	5'-GAT CTG GTC TGT GTG CTC CTG-3'	61.8	21
TRPM8	Left	5'-GCC CAG TGA TGT GGA CAG TA-3'	59.4	20
TRPM8	Right	5'-GGA CTC ATT TCC CGA GAA GG-3'	59.4	20
TRPM6	Left	5'-GCA AGA ACT GGC TTT CCG TG-3'	59.4	20
TRPM6	Right	5'-ATC CGG GTC CTC TTG CAT CT-3'	59.4	20
TRPM7	Left	5'-AGA CGC TTT CCG ATA GAT GG-3'	57.3	20
TRPM7	Right	5'-CTA TCC AGG ATT TCT GGG ACA T-3'	58.4	22
β-Actin	Left	5'-CCC GCG AGT ACA ACC TTC T-3'	58.8	19
β-Actin	Right	5'-CGT CAT CCA TGG CGA ACT-3'	56.0	18

Histopathological examination

After euthanasia, rats were necropsied and liver tissues were taken into 10% buffered formalin solution. The samples were then subjected to routine follow-up procedures and embedded in paraffin blocks. The 5 µm sections from the blocks were stained with Hematoxylin-Eosin for necrotic and degenerative changes. Sections examined under light microscopy were evaluated as none (-), mild (+), moderate (++) and severe (+++).

Data Analysis and Statistical analysis

The data were sorted out by utilizing Rotor-Gene Q Software, and the positive number chambers were corrected to estimate the actual number of copies. Described numbers were used to determine the number of copies in the original sample. As the housekeeping gene for normalization of the expressions, Beta Actin was used (Normalization= CT of Beta Actin/ CT of Gene). The expression levels in lidocaine group, I/R group, and I/R-lidocaine group were compared. The expression levels of TRPM genes, with and without treatment, in each liver tissue were compared within itself.

Data were analyzed using GraphPad Prism 5 program. Data were expressed as mean values ± standard error of the mean (SEM). For normally distributed data, one-way analysis of variance (ANOVA) with the Bonferroni's multiple comparison post-test was used to test for significant differences. Histopathological data were assessed with the Pearson Chi-Square test which was utilized to compare ratios. P-values < 0.05 were considered as statistically significant.

Results

TRPM2, TRPM6, TRPM7, and TRPM8 Expressions

The Expression levels of TRPM2, TRPM6, TRPM7, and TRPM8 were shown in Table 2 and Figure 1.

The expression levels of TRPM2 were significantly higher in liver-I/R group compared to sham and lidocaine groups ($p<0.05$, $p<0.000$, respectively), TRPM8 genes were significantly higher in liver-I/R group compared to sham and lidocaine groups ($p<0.05$, $p<0.05$, respectively). However, the expression levels of TRPM6 gene were significantly higher in liver-I/R group compared to sham, lidocaine, and I/R-lidocaine groups ($p<0.05$, $p<0.01$, $p<0.05$, respectively), TRPM7 genes were significantly higher in liver-I/R group compared to sham, lidocaine, and I/R-lidocaine groups ($p<0.05$, $p<0.000$, $p<0.05$, respectively). The normalized CT± SD of TRPM2 values were 0.996±0.00, 0.980±0.01, 1.074±0.00 and 1.019±0.01 for sham, lidocaine, liver-I/R and I/R-lidocaine groups, respectively (Figure 1). The highest expression level of TRPM6 gene was in the liver-I/R group (Normalized CT ± SD: 1.218±0.01) and the values of normalized CT± SD were 1.148±0.01, 1.127±0.01, and 1.141±0.01 for sham, lidocaine, and I/R-lidocaine groups, respectively (Figure 1). TRPM7 expression was modest in the lidocaine group (Normalized CT± SD: 1.189±0.01) and the values of normalized CT± SD were 1.239±0.01, 1.344±0.01, and 1.237±0.01 for sham, liver-I/R, and I/R-lidocaine groups, respectively (Figure 1). For TRPM8 gene, the values of expressions were 1.156±0.01, 1.152±0.02, 1.249±0.02 and 1.197±0.01 in hepatocytes from the sham, lidocaine, liver-I/R and I/R-lidocaine groups, respectively (Figure 1) (Table 2).

Table 2. Statistical data of gene expression results(Mean±SD)

Genes	Sham (n=8)	Lid.(n=8)	I/R (n=8)	Lid+I/R (n=8)
TRPM2	0,99±0,0	0,98±0,0^{b***}	1,07±0,0^{a**}	1,01±0,0
TRPM6	1,14±0,0	1,12±0,0^{b**}	1,21±0,0^{a*}	1,14±0,0^{b*}
TRPM7	1,23±0,0	1,18±0,0^{b***}	1,34±0,0^{a*}	1,23±0,0^{b*}
TRPM8	1,15±0,0	1,15±0,0^{b*}	1,24±0,0^{a*}	1,19±0,0

I/R: Ischemia- reperfusion; Lid: Lidocaine; [a]: compared with Sham group; [b]: compared with I/R group. *: p<0.05; **: p<0.01; ***: p<0.001

Lidocaine and Sham groups had normal liver histology (Figure 2A-B). A statistically significant difference was found between ischemia-reperfusion and ischemia-reperfusion+lidocaine groups ($p<0.05$). Severe levels of necrotic/degenerative changes and intense hemorrhagic areas were observed in the livers of rats in the ischemia-reperfusion group (Figure 2C). Necrotic/degenerative changes in the liver of rats in the ischemia-reperfusion group with lidocaine were found to be less than in the ischemia-reperfusion group alone (Figure 2D) (Table 3).

Table 3. Statistical data of gene expression results(Mean±SD)

	Sham (n=8)	Lid.(n=8)	I/R (n=8)	Lid+I/R (n=8)
Cellular swelling	1.47±0.2	1,10±0,0^{b**}	2,75±0,2^{a*}	1,60±0,1^{b**}
Congestion	1.90±0.3	1,71±0,0^{b**}	3,65±0,2^{a*}	3,31±0,1^{c**}
Polymorph nuclear leukocytes	1.18±0.1	1,14±0,1^{b**}	1,77±0,3^{a*}	1,10±0,3^{b**}
Apoptosis	0.28±0.1	1,14±0,1	0,57±0,2	0.34±0.2

I/R: Ischemia- reperfusion; Lid: Lidocaine; [a]: compared with Sham group; [b]: compared with I/R group. [c]: compared with Lid. group.*: p<0.05; **: p<0.01

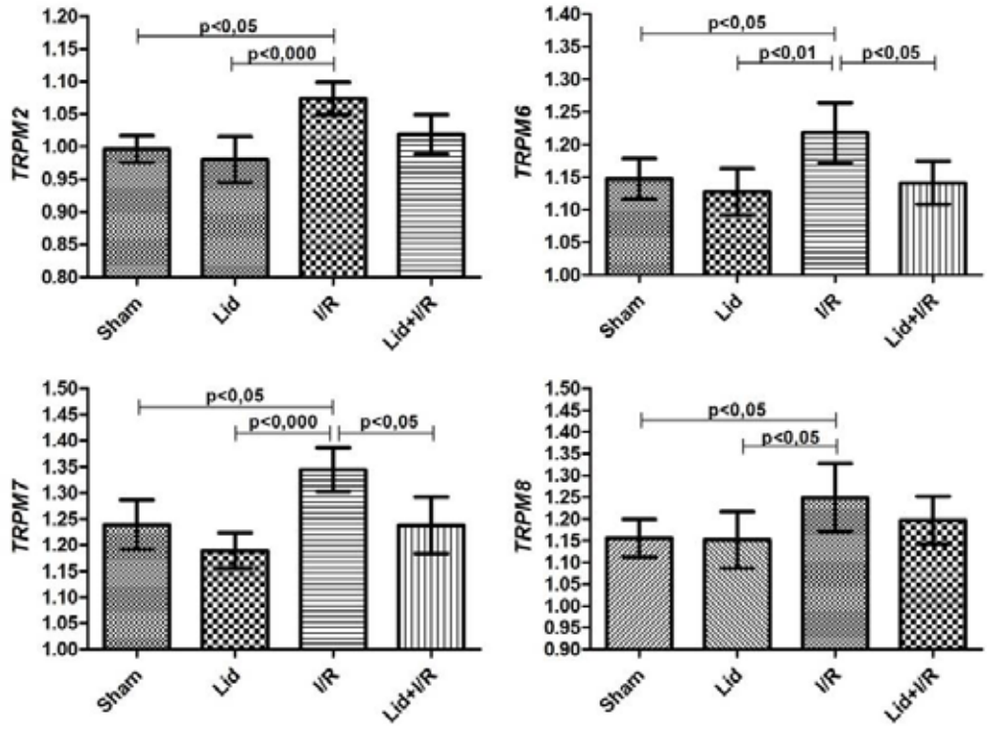

Figure 1. The expression levels of TRPM2, TRPM6, TRPM7 and TRPM8 genes

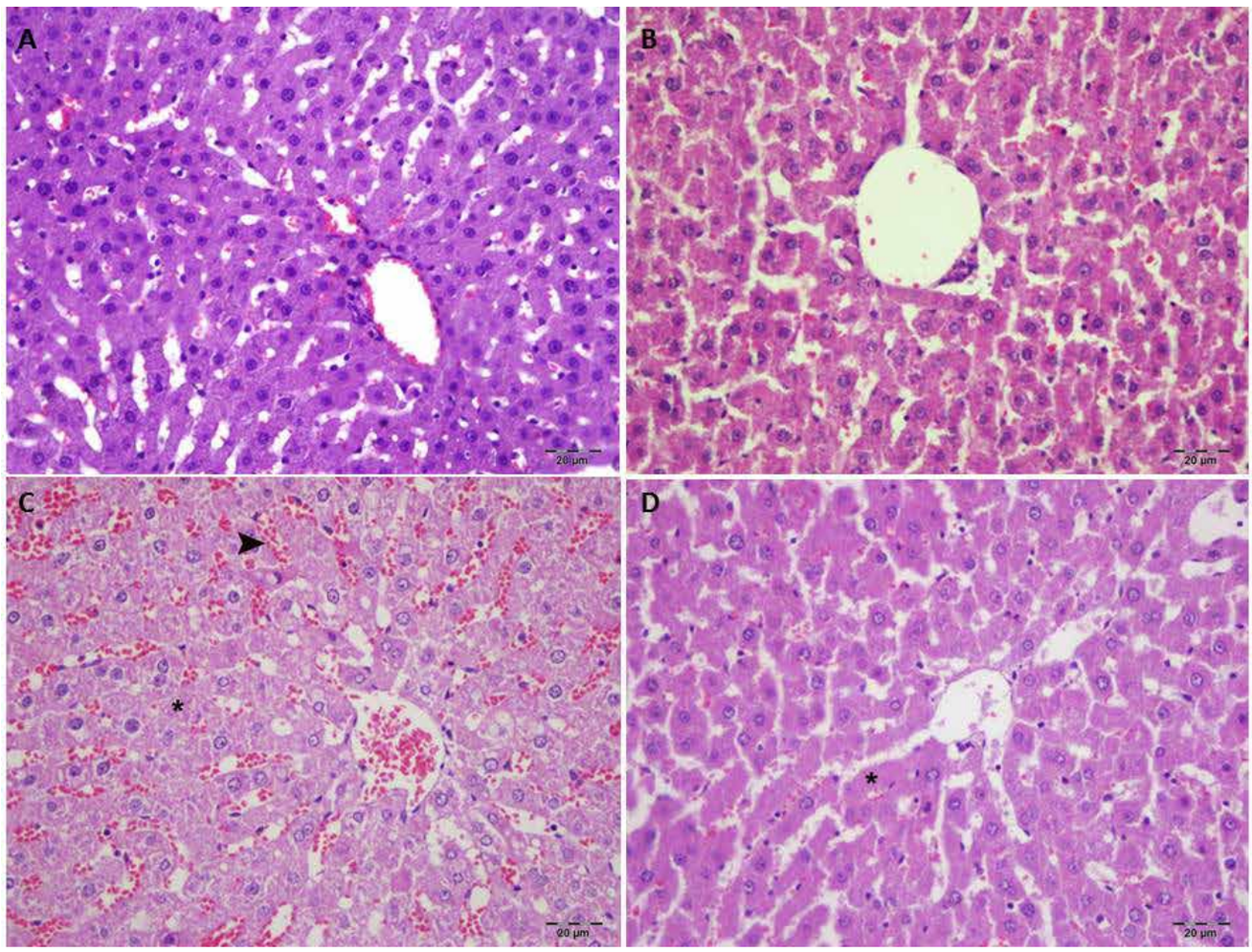

Figure 2. A: Shame group. Normal histological appearance. B: Lidocaine group. Normal histological appearance. C: Ischemia-Reperfusion group. Severe levels of necrotic/ degenerative changes in hepatocytes (*) and hemorrhagic areas (arrowheads). D: Ischemia-Reperfusion + Lidocaine group. Moderate necrotic / degenerative changes in hepatocytes (*).

Discussion

In the current study, we determined the effect of lidocaine on expression of TRPM2, TRPM6, TRPM7 and TRPM8 channels. Our data showed that the levels of TRPM2, TRPM6, TRPM7 and TRPM8 expressions changed in I/R when pre-administration of lidocaine occurred. We thought that these changes including TRPM2-6-7-8 expression levels can be related to the concentration of sodium ion changes during exposed lidocaine rats with I/R. Moreover, this report is the first investigation about the mentioned subject on rat liver with I/R.

The restriction of nutrient and oxygen causes the efflux of calcium that causes necrotic or apoptotic cell death at ischemia [17]. The reentering of oxygen and nutrient renovates mitochondrial membrane potential at reperfusion [18]. Some studies have described the protective effects of lidocaine in I/R injury for heart, lung, and brain tissues [19, 20]. Underlying mechanisms of these processes, lidocaine modulates inflammatory response or attenuates apoptotic cell death. The increases of calcium in the extracellular matrix (ECM) affect sodium and potassium conductance versus voltage curves. The added high calcium leads to an increase in the time to peak of sodium level at medium [15]. We thought that the treatment of I/R rats with lidocaine, TRPM calcium channel gene expression level can be affected by the change of sodium level due to injected lidocaine.

Our data implicated that TRPM2, TRPM6, TRPM7, and TRPM8 genes were expressed in the liver tissue. Sixty minutes after liver reperfusion, TRPM6 and TRPM7 expression levels were statistically significantly decreased in the group exposed to lidocaine. In the group exposed to lidocaine, a decrease in TRPM2 and TRPM8 gene expressions is observed. However, this difference was not statistically significant.

TRPM2 activation leads to an increase in intracellular calcium levels [21]. Dusmez et al. showed increased TRPM2 expression in lidocaine groups from liver renal tissue [22]. According to our data, TRPM2 expression level changes in liver tissue with exposed lidocaine. On the other hand, our unpublished data showed that treatment with verapamil which blocks calcium channel, affects increased TRPM2 expression level. Underlying these situations, TRPM2 is affected by verapamil that leads to calcium concentration; however, sodium level which is changed by lidocaine can attenuate TRPM2 expression level.

TRPM6 and TRPM7 regulate magnesium and calcium homeostasis and they are expressed by every mammalian cell [23]. We showed that TRPM6 and TRPM7 expression levels were evaluated in liver tissue with exposed lidocaine. Zhang et al. reported that TRPM6 and TRPM7 expression levels were increased in sodium/ischemia groups and they suggested that TRPM2 and TRPM6 have a role in preventing apoptosis [24]. Furthermore, TRPM7 has been found to be involved in delayed neuronal death after ischemia [25]. Our results correlate with some data of some studies but not with all. Thus, we can say that decreased TRPM6 and TRPM7 expression levels protect liver cells from apoptosis in treatment with lidocaine.

TRPM8 is activated by low temperatures (threshold 25 0C) and by exposure to cooling compounds, such as menthol [26]. According to our data, TRPM8 expression level decreased in liver tissue with exposed lidocaine. However, this decrease was not statistically significant.

In conclusion, in this study, we evaluated expression changes of TRPM2/8 and TRPM6/7 genes in hepatocytes of rats which were exposed to I/R after administration of lidocaine. The increase of calcium in the ECM affects sodium and potassium conductance versus voltage curves. The added high calcium leads to an increase in the time to peak of sodium level at medium [15]. However, all calcium channels including TRPs, ryanodine, and calcium pumps should be investigated. We think that administration of lidocaine may protect liver from ischemia-reperfusion injury by reducing increased TRPM2/8 and TRPM6/7 genes expression in Liver I/R injury and liver transplantation.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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